1: Expert Opin Biol Ther 2002 Jan;2(1):3-24

HSP90 as a new therapeutic target for cancer therapy: the story unfolds.

Workman P, Maloney A.

CRC Centre for Cancer Therapeutics, Institute of Cancer Research, Block E, 15 Cotswold Road, Sutton, Surrey SM2 5NG, UK. paulw@icr.ac.uk

Current anticancer drug development strategies involve identifying novel molecular targets which are crucial for tumourigenesis. The molecular chaperone heat shock protein (HSP) 90 is of interest as an anticancer drug target because of its importance in maintaining the conformation, stability and function of key oncogenic client proteins involved in signal transduction pathways leading to proliferation, cell cycle progression and apoptosis, as well as other features of the malignant phenotype such as invasion, angiogenesis and metastasis. The natural product HSP90 inhibitors geldanamycin and radicicol exert their antitumour effect by inhibiting the intrinsic ATPase activity of HSP90, resulting in degradation of HSP90 client proteins via the ubiquitin proteosome pathway. Anticancer selectivity may derive from the simultaneous combinatorial effects of HSP90 inhibitors on multiple cancer targets and pathways. 17-allylamino, 17-demethoxygeldanamycin (17AAG), a geldanamycin derivative, showed good activity and cancer selectivity in preclinical models and has now progressed to Phase I clinical trial in cancer patients with encouraging initial results. Phase II trials including combination studies with cytotoxic agents are now being planned and these should allow the therapeutic activity of 17AAG to be determined. Second generation HSP90 inhibitors may be designed to overcome some of the drawbacks of 17AAG, including limited oral bioavailability and solubility. They could also be engineered to target specific functions of HSP90, which may not only provide greater molecular selectivity and clinical benefit but may also increase understanding of the complex functions of this molecular chaperone. HSP90 inhibitors provide proof of concept for drugs directed at HSP90 and protein folding and this principle may be applicable to other medical conditions involving protein aggregation and stability.

PMID: 11772336 [PubMed - in process]

Display Abstract Sort Save Text Clip Add Order

i686-pc-linux-gnu Oct 31 2002 15:09:13

☐ 1: Cancer Res 2001 Apr 1;61(7):2945-52

Inhibition of heat shock protein 90 function by ansamycins causes the morphological and functional differentiation of breast cancer cells.

Munster PN, Srethapakdi M, Moasser MM, Rosen N.

Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, New York 10021, USA.

17-(Allylamino)-17-demethoxygeldanamycin (17-AAG) is an ansamycin antibiotic that binds to a conserved pocket in Hsp90 and induces the degradation of proteins that require this chaperone for conformational maturation. 17-AAG causes a retinoblastoma (RB)-dependent G1 block in cancer cells and is now in clinical trial. In breast cancer cells, G1 block is accompanied by differentiation and followed by apoptosis. The differentiation is characterized by specific changes in morphology and induction of milk fat proteins and lipid droplets. In cells lacking RB, neither G1 arrest nor differentiation occurs; instead, they undergo apoptosis in mitosis. Introduction of RB into these cells restores the differentiation response to 17-AAG. Inhibitors of the ras, mitogen-activated protein kinase, and phosphatidylinositol 3-kinase pathways cause accumulation of milk fat proteins and induction of lipid droplets when associated with G1 arrest but do not cause morphological changes. Thus, regulation of Hsp90 function by 17-AAG in breast cancer cells induces RB-dependent morphological and functional mammary differentiation. G1 arrest is sufficient for some but not all aspects of the phenotype. Induction of differentiation may be responsible for some of the antitumor effects of this drug.

PMID: 11306472 [PubMed - indexed for MEDLINE]

i686-pc-linux-gnu Oct 31 2002 15:09:13